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EXAMINER	
SULLIVAN, DANIEL M	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/631,152	Applicant(s) WOLFF ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on th cover sh t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *18-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

This is a First Office Action on the Merits of the application filed August 2, 2000, which claims benefit of 60/146,824 filed August 2, 1999. This Office Action is a response to the reply filed October 18, 2002 (Paper No. 12). Claims 1-33 are pending in the application.

Election/Restrictions

In response to the restriction requirement, Applicants "provisionally request examination of Group I: claims 1-17". This response is understood to be an election without traverse of Group I as set forth in the restriction requirement mailed September 30, 2002 (Paper No. 10).

Claims 18-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims of the instant application are directed to a process for nucleic acid delivery to a cell, comprising attaching a compound to the nucleic acid within the expressible sequence and delivering the nucleic acid to a cell where the expressible sequence is expressed. In some embodiments, the attached compound is limited to a nuclear localizing signal, a ligand that binds a receptor, a releasing signal, an enhanced immune response molecule, an antigen, an antibody, a hapten, a membrane active compound, a peptide, a polymer, a polyion and a fluorescent compound. Given their broadest reasonable interpretation the claims encompass a method for nucleic acid delivery wherein any and all compounds or any and all nuclear localizing signals, any and all ligands that binds a receptor, any and all releasing signals, any and all enhanced

immune response molecules, any and all antigens, any and all antibodies, any and all haptens, any and all membrane active compounds, any and all peptides, any and all polymers, any and all polyions and any and all fluorescent compounds.

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Column 3, page 71434). In the instant case, the compound attached to the nucleic acid is a critical element of the claimed method; therefore, an adequate description of the method requires adequate description of the compound attached to the nucleic acid in step (b).

The compounds encompassed within the claims constitute a widely divergent genus of molecules, which can be attached *within the expressible sequence* of a nucleic acid molecule without disrupting expression from the expressible sequence. For reasons set forth in detail herein below, the attributes common to the genus compound capable of being attached within an expressible sequence without disrupting expression are unknown in the art and therefore unpredictable.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the instant case, the disclosure sets forth a variety of classes of molecules that could be attached to a DNA (see especially the paragraph bridging pages 1 and 2) although the description does not distinguish those molecules having the ability to be incorporated within an expressible sequence without disrupting expression of the sequence. The disclosure also provides reduction

to practice of the method wherein the attached molecule is rhodamine, DNP, digoxin, biotin, and a peptide nuclear localization sequence (see Examples 1-4 and 6). However, given the very large and divergent nature of the genus of compounds encompassed within the claims, the examples provided are far from representative.

According to the Guidelines on Written description, identifying characteristics include, "structure or other physical and/or chemical properties,...functional characteristics coupled with a known or disclosed correlation between function and structure or... a combination of such identifying characteristics..." (Federal Register, Vol. 66, No. 4, page 1106, column 3, second full paragraph). In the instant case, the disclosure fails to provide no description whatsoever of the structural characteristics that are common to all molecules having the desired function or that correlate with the function.

An adequate written description of a compound requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the compound itself. It is not sufficient to define a compound solely by its principal biological property, i.e. it does not prevent expression of the expressible sequence, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all compounds that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* compounds or nuclear localizing signals, ligands that binds a receptor, releasing signals, enhanced immune response molecules, antigens, antibodies, haptens, membrane active compounds, peptides, polymers, polyions and fluorescent compounds capable of being incorporated into an expressible sequence without disrupting expression. Therefore, only the methods comprising the compounds reduced to practice (i.e. rhodamine, DNP, digoxin, biotin, and the peptide nuclear localization sequence CPKKKRKVEDG) meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for nucleic acid delivery to a cell *in vitro*, comprising: (a) preparing a nucleic acid molecule having an expressible sequence; (b) attaching a compound to the nucleic acid molecule tithing the expressible sequence, utilizing a modifying chemical attachment; and, (c) delivering the nucleic acid to a cell where the expressible sequence is expressed, wherein said compound is selected from the group consisting of rhodamine, DNP, digoxin, biotin, and the peptide nuclear localization sequence CPKKKRKVEDG, does not reasonably provide enablement for a process for nucleic acid delivery to a cell *in vivo* or a process for nucleic acid delivery to a cell *in vitro* wherein the compound is *any* and *all*

compounds or nuclear localizing signals, ligands that binds a receptor, releasing signals, enhanced immune response molecules, antigens, antibodies, haptens, membrane active compounds, peptides, polymers, polyions and fluorescent compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The claims are directed to a process for nucleic acid delivery to a cell, comprising: preparing a nucleic acid molecule having an expressible sequence; attaching a compound to the nucleic acid molecule *within the expressible sequence*, and delivering the nucleic acid to a cell where the expressible sequence is expressed.

Breadth of the claims: As described herein above, the claims broadly encompass a method of using any and all compounds that can be attached within the expressible sequence of a nucleic acid molecule without preventing expression of the expressible sequence. It is also clear from the disclosure that the method encompasses delivery of a nucleic acid sequence *in vivo* for the purpose of gene therapy (see especially beginning the second full paragraph on page 2 and

continuing through the first full paragraph on page 5). The enabling disclosure must therefore teach the skilled artisan how to use the claimed method for *in vivo* gene therapy.

State of the prior art and level of predictability in the art: With regard to the method directed to therapeutic expression of a nucleic acid *in vivo*, at the time of filing *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, "... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the

delivery of exogenous DNA and its processing by target cells require the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic

gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future"**, beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claims of the instant application are not limited to treatment of any particular condition and thus encompass methods of treating any and all conditions that might be amenable to gene therapy. However, Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however,

even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels.

Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

With regard to practicing the disclosed method using any and all compounds, teachings in the prior art published as recently as late 1999 indicate that obtaining expression from a labeled nucleic acid molecule is highly unpredictable. Felgner *et al.* (1999) WO 99/13719 teaches that standard methods of labeling DNA using fluorescently tagged nucleotides do not allow detection of structurally and functionally intact plasmid in a real-time fashion in viable cells (paragraph bridging pages 1 and 2) and that "all of the technologies...for chemically modifying plasmid DNA result in DNA damage and interfere with its transcriptional activity" (sentence bridging pages 1 and 2). Neves *et al.* (2000; published online December 15, 1999) *Bioconjugate Chem.* 11:51-55 demonstrated that reporter gene expression was greatly reduced by labeling DNA with

p-azido-tertrafluorbenzylamido-lissamine and abolished by labeling DNA with rhodamine labeled nucleotides (see especially the fourth full paragraph on page 53, and Figure 2 and the caption thereto). Neves *et al.* suggests that the poor expression obtained with labeled vectors might result from interference with the transcription apparatus (see especially the fourth paragraph in the second column on page 54). or sequestration or degradation of the labeled molecules (see especially the first paragraph on page 55). Zelpahti *et al.* (1999) *Hum. Gene Therap.* 10:15-24 teaches that, "the methods that have been employed to directly modify DNA either reduce or destroy its ability to be transcribed. In addition, the available approaches to chemically modify plasmid, which utilize photolysis, nick translation, or the use of chemically active nucleotide analogs, attack the DNA randomly so that the final product is chemically heterogeneous and poorly defined" (paragraph bridging pages 15 and 16).

These teachings from the relevant art demonstrate that obtaining expression of a gene from a nucleic acid molecule that has been chemically modified to incorporate a label was highly unpredictable at the time the instant application was filed.

Amount of direction provided by the inventor existence of working examples: Given the art recognized unpredictability of obtaining expression from a nucleic acid molecule comprising a compound covalently incorporated in a expressible sequence, the skilled artisan is dependent upon the teachings of the specification to provide guidance such that compounds that can be incorporated into an expressible sequence without preventing expression can be identified without undue experimentation. The instant disclosure sets forth a variety of classes of molecules that could be attached to a DNA (see especially the paragraph bridging pages 1 and 2) but does not distinguish those molecules having the ability to be incorporated within an expressible

sequence without disrupting expression of the sequence. The disclosure further provides reduction to practice of the method wherein the attached molecule is rhodamine, DNP, digoxin, biotin, and a peptide nuclear localization sequence (see Examples 1-4 and 6). However, given the very large and divergent nature of the genus of compounds encompassed within the claims, the examples do not enable the skilled artisan to identify compounds that could be used in the claimed method without resorting to blind trial and error experimentation to test each and every candidate compound.

With regard to the method as it is directed to *in vivo* delivery, given the art recognized unpredictability of obtaining expression from a nucleic acid delivered *in vivo* at a level and for a duration adequate to obtain a useful phenotype (i.e. therapeutic correction of a defect), the skilled artisan is dependent upon the specification to teach how a product having real-world utility can be produced according to the claimed method. The disclosure provides methods of delivering a nucleic acid covalently modified with digoxin (Examples 3 and 6), biotin (Example 4), and the nuclear localization sequence CPKKKRKVEDG (Example 5). However, the findings with regard to level of expression are presented in arbitrary units as compared with results obtained with naked DNA and expression was measured at only a single time point, one day after administration. The disclosure provides no evidence whatsoever that the barriers to obtaining expression of sufficient level and duration to treat any condition have been addressed by the claimed method.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is very high, teachings in the relevant art indicate that obtaining expression from a nucleic acid labeled according to the teachings of

the specification is highly unpredictable. The disclosure fails to provide any teaching that would enable the skilled artisan to practice the invention commensurate with its full scope without resorting to blind trial and error experimentation to identify each and every compound to be used according to the claimed method. Therefore, in order to practice the full scope of the claimed invention, the skilled artisan would be required to test each and every compound or nuclear localizing signal, ligand that binds a receptor, releasing signal, enhanced immune response molecule, antigen, antibody, hapten, membrane active compound, peptide, polymer, polyion and fluorescent compound on an individual basis to identify those capable of being incorporated into an expressible sequence without disrupting expression. Given the teachings from the art indicating that the number of compounds that would be useful in the claimed method is small and the very large genus of compounds to be tested, the amount of experimentation required would certainly be undue.

With regard to practicing the invention *in vivo*, again, although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods of the instant invention without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples, the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the

teachings of the specification and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

Therefore, only the methods comprising the compounds reduced to practice (i.e. rhodamine, DNP, digoxin, biotin, and the peptide nuclear localization sequence CPKKKRKVEDG) practiced *in vitro* meet the requirements for enablement under 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, and 14-17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in their use of the indefinite article "a" in referring to the claim from which they depend. As written, the claims suggest that the base claim is directed to multiple distinct processes, one or more of which are further limited by the dependent claim. It would appear that Applicant intends that the claims are directed to "the" process recited in the base claim and amending the claims accordingly would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claimed method. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 1-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Leahy *et al.* (1996; IDS Paper No. 4, Item #5) as evidenced by Pierce Chemical Technical Library publication "Other Biotinylation Reagents: Immunopure® Photoactivatable Biotin" available at http://www.piercenet.com.

Claim 1 is directed to a process for nucleic acid delivery to a cell, comprising; a) preparing a nucleic acid molecule having an expressible sequence b) attaching a compound to the nucleic acid molecule within the expressible sequence, utilizing a modifying chemical attachment; and, c) delivering the nucleic acid to a cell where the expressible sequence is expressed.

Leahy *et al.* teaches a process for nucleic acid delivery to a cell, comprising; a) preparing a nucleic acid molecule having an expressible sequence b) attaching a compound to the nucleic acid molecule within the expressible sequence, utilizing a modifying chemical attachment; and, c) delivering the nucleic acid to a cell where the expressible sequence is expressed (see

especially the first full paragraph on page 546, the first full paragraph in the second column of page 547, and Figures 2 and 3 and the captions thereto).

Claim 2 is directed to the process of claim 1 wherein the level of expression obtained is greater than 40% of the level of expression obtained from the expressible sequence not having a modifying chemical attachment.

In Figures 2 and 3, and in the second full paragraph on page 549, Leahy *et al.* demonstrates CAT expression obtained using the disclosed method that averages 40% of the expression obtained from the expressible sequence not having a modifying chemical attachment. Given the standard error shown in Figures 2 and 3, their expression encompasses expression greater than 40% of the level of expression obtained from the expressible sequence not having a modifying chemical attachment

Claim 3 is directed to the process of claim 2 wherein compound comprises a nucleic acid transfer enhancing signal; claim 4 is directed to the process of claim 3 wherein the nucleic acid transfer enhancing signal is selected from the group consisting of a nuclear localizing signal, a ligand that binds a receptor, and a releasing signal; and claim 5 is directed to the process of claim 1 wherein the compound is selected from a group of consisting of an enhanced immune response molecule, an antigen, an antibody, a hapten, a membrane active compound, a peptide, a polymer, a polyion, and a fluorescent compound..

In the third full paragraph on page 550, Leahy *et al.* teaches that their method can be used with a variety of nucleic acid transfer enhancing signals including peptide nuclear localization signals, fluorescent compounds (see especially the third full paragraph on page 550) and ligands (see especially the first paragraph in the second column on page 549).

Claim 6 is directed to the process of claim 1 whereby the compound is attached to the N7 position of guanine; claim 7 is directed to the process of claim 1 wherein the step of attaching comprises modifying the nucleic acid using an alkylating molecule; claim 8 is directed to the process of claim 7 wherein the alkylating molecule is selected from the group consisting of a mustard and a 3-membercd ring system; claim 9 is directed to the process of claim 8 wherein the mustard is selected from the group consisting of a nitrogen mustard and a sulfur mustard; and claim 13 is directed to the process of claim 1 wherein the nucleic acid consists of double-stranded and single stranded DNA.

Leahy teaches a method wherein the compound is attached to a double-stranded DNA using an alkylating molecule that is a nitrogen mustard and non-specifically incorporated and therefore incorporated at the N7 position of guanine as well as other positions (see especially the attached manufacturer's description of the biotinylating reagent used by Leahy *et al.*).

The process, compound and DNA taught by Leahy *et al.* are the same as those taught in the instant application; therefore, the limitations of the claims are met by Leahy *et al.*

Claims 1, 7 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ireland *et al.* (1987) *FEBS Lett.* 212:173-176.

The limitations of the claims are set forth herein above. Ireland *et al.* teaches a process for nucleic acid delivery to a cell, comprising; a) preparing a nucleic acid molecule having an expressible sequence; b) attaching a compound to the nucleic acid molecule within the expressible sequence, utilizing a modifying chemical attachment; and, c) delivering the nucleic acid to a cell where the expressible sequence is expressed. Ireland *et al.* further teaches

modification of the DNA molecule which comprises alkylation and modification of a double stranded DNA (see especially the paragraph bridging pages 173 and 174, the second paragraph on page 174 and Tables 1-3 and the captions thereto).

The process and DNA taught by Ireland *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Ireland *et al.*

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
December 6, 2002

JAMES KETTER
PRIMARY EXAMINER